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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,128	02/27/2002	Jacques Briand	P51032	9830

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EXAMINER	
SHIBUYA, MARK LANCE	
ART UNIT	**PAPER NUMBER**
1639	

NOTIFICATION DATE	DELIVERY MODE
09/24/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

US_cipkop@gsk.com

Office Action Summary	Application No.	Applicant(s)	
	10/070,128	BRIAND, JACQUES	
	Examiner	Art Unit	
	Mark L. Shibuya, Ph.D.	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/23/2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8,10,17 and 18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-8,10,17 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/23/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Application 10070128: Claims 1, 3-8, 10, 17 and 18 are pending and examined.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 7/23/2007 has been entered.

Priority

3. This application, 10/070,128, filed 2/27/2002, is the national stage entry of PCT/US00/26949, filed 9/29/2000, which claims benefit of Provisional application 60/156,557, filed 9/29/1999.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on 7/23/07 was filed after the mailing date of the Supplemental Notice of Allowability on 7/9/2007. The submission is in compliance with the provisions of 37 CFR 1.97.

Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1, 3-8, and 10 rejected under 35 U.S.C. 102(b) as being anticipated by Chiyoda et al., Chem. Pharm. Bull. (1998) Vol. 46 (4), pp. 718-720, (IDS entered 7/23/2007).

The amended claims are drawn to a method of identifying at least one chemical compound that interact with an enzyme comprising the steps of: a) mixing a substrate of said enzyme with at least one said chemical compound; b) generating a first NMR spectrum that displays either a chemical shift in the first dimension or a chemical shifts in the other dimension of said substrate in step a);

c) exposing the mixture of said substrate or product and at least one said chemical compound in step a) to said enzyme for one or more incubation times; d) generating a second NMR spectrum that displays either a chemical shift in the first dimension or a chemical shifts in the other dimension of substrate in step a) that has been exposed to said enzyme in step c) in the presence of at least one chemical compound in step a); e) comparing said first NMR spectrum and second NMR spectrum after one or more said incubation times in step c) to determine at least one difference between said first NMR spectrum and second NMR spectrum, the differences observed along either or both chemical shift dimensions identifying transformation of said substrate and classifying the presence of at least one said chemical compounds that interact with said enzyme.

Chiyoda et al., Chem. Pharm. Bull. (1998) Vol. 46 (4), pp. 718-720, throughout the publication, teach ^{13}C-NMR measurements of the time course of decrease in the signal of the substrate ^{13}C-urea in the presence of the enzyme urease and also in the presence of a plurality of urease inhibitors.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which

said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1, 3-8, 10, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chiyoda et al., Chem. Pharm. Bull. (1998) Vol. 46 (4), pp. 718-720, (IDS entered 7/23/2007), Fesik et al., (WO 98/48264), (of record), and in view of Peters et al., Biochemistry 1992, Vol. 31, pp. 10024-10030, (of record).

Chiyoda et al., are relied upon as above.

Chiyoda does not teach NMR methods of identifying chemical that interact with enzymes, comprising chemicals attached to a substrate, multiwell vessels, or quenching.

Fesik et al., (WO 98/48264), throughout the publication, and at p. 1, lines 2-4, p. 2, line 23-p. 3, line 12, p. 4, line 18-p.4, line 33, p. 7, line 32-p. 8, line 37, p. 10, lines 10-19, p. 10, line 35-p. 11, line 2, teaches: a) generating a first T2- or diffusion-filtered proton spectrum of one or a mixture of chemical compounds; b)

exposing one or a mixture of chemical compounds to the target molecule; c) generating a second T2- or diffusion filtered proton spectrum of one or a mixture of chemical compounds that has been exposed to the target molecule in step (b); and d) comparing said first and second T2- or diffusion-filtered proton spectra to determine differences between said first and said second spectra, the differences identifying the presence of one or more compounds that are ligands which have bound to the target molecule. Additional steps comprise the steps of e) generating a T2- or diffusion-filtered proton spectrum of each compound in the mixture f) exposing each compound in the mixture individually to the target molecule, g) generating a T2- or diffusion-filtered proton spectrum of each compound in the mixture after exposure to the target molecule h) comparing each spectrum generated in step g) to the first spectrum generated from the target molecule alone to determine differences in any of those compared spectra, the differences identifying the presence of a compound that is a ligand which has bound to the target molecule; wherein the target is a polypeptide, which is a biomolecule. Fesik et al. teaches use of a sample changer with a total of 60 samples that can be run unattended and computer programs to facilitate transfer and automatic processing of multiple one-dimensional NMR data.

Fesik et al., (WO 98/48264), at p. 1, lines 16-20, discloses that the prior art teaches assaying enzyme reactions. Fesik et al., (WO 98/48264) at p. 2, lines 33-37, teaches that screening more than compound or a mixture of compounds prior to exposing the mixture to the target molecule, is desirable

because an active compound can be identified immediately if the spectrum of the active compound in the absence of the target molecule is known.

Peters et al., throughout the publication, and describe a method of identifying at least one chemical compounds that interact with an enzyme comprising the steps of: at e.g., p 10027, para 5 and Table I, fn.1, p. 10025, para 3, 4, 13, teach determining NMR data for samples of the enzyme phospholipase A2 (PLA) and fully deuterated *n*-dodecylphosphocholine (DPC) in micellar form, reading on a substrate of PLA, and the inhibitor (R)-2-(dodecanolylamino)hexanol-1-phosphoglycol. Peters et al., at e.g., p. 10028, para 7-10, p. 10028, para 15, p. 10029, para 2-3, teach that upon binding of the enzyme, substrate and inhibitor, thereby forming a ternary complex, there are pronounced changes in the chemical shift of the enzyme's backbone, which are probably due to conformational changes. Peters et al., at pp. 10025, second column-10027, first column, and Fig. 2, disclose an NMR method comprising first and second NMR spectrum displaying 1H and 15N chemical shifts in a first and second dimensions.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have made and used NMR methods of identifying compounds that interact with enzymes, wherein an enzyme substrate or product is mixed with at least one said chemical compounds; and wherein the mixture of said substrate or product and at least one said chemical compound, is exposed, subsequently, to said enzyme.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have made and used NMR methods comprising first and second NMR spectrum displaying chemical shifts in a first and other dimension selected from the group consisting of 1H, 3H, 11B, 13C, 15N, 19F 29S and 31P, (as in claims 5 and 8).

The use of well plates for storage of compounds was well known in the art at the time of filing. One of ordinary skill in the art would have been motivated to do so due to the ease of use of such formats. It was also well known in the art to quench certain reactions after a period of time, depending upon the reaction of interest and measurement technique. Thus, it would be well within the ordinary skill in the art to perform such a step depending on the specific reaction. One would be motivated to carry out such a step in order to monitor a reaction after a certain period of time (measure reaction progress, etc.).

One of ordinary skill in the art would have been motivated to make and use NMR methods wherein an enzyme substrate or product is mixed with at least one said chemical compounds because Peters et al., at e.g., p. 10028, para 7-10, p. 10028, para 15, p. 10029, para 2-3, teach that it is desirable to measure binding of the enzyme, substrate and inhibitor, in a ternary complex, in order to achieve and detect pronounced changes in the chemical shift of the enzyme's backbone, which are probably due to conformational changes. One of ordinary skill in the art would have been motivated to make and use NMR methods comprising mixing a substrate or product of said enzyme with at least one said chemical compounds; and then exposing the mixture of said substrate or product

and at least one said chemical compound, to said enzyme, because Fesik et al., (WO 98/48264) at p. 2, lines 33-37, teaches that screening more than compound or a mixture of compounds prior to exposing the mixture to the target molecule, is desirable because an active compound can be identified immediately if the spectrum of the active compound in the absence of the target molecule is known.

One of ordinary skill in the art would have been motivated to make and use NMR methods It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have made and used NMR methods comprising first and second NMR spectrum displaying chemical shifts in a first and other dimension selected from the group consisting of 1H, 3H, 11B, 13C, 15N, 19F 29S and 31P, (as in claims 5 and 8) because Peters et al., at p. 10025, teach the use of high-resolution NMR spectroscopy to obtain detailed information about the structure of the ternary complex of protein bound to a micelle, reading on a substrate, and containing a single inhibitor molecule in its active site.

One of ordinary skill in the art would have had a reasonable expectation of success in using such methods because Peters and Fesik teach the NMR identification of compounds that interact with proteins, including enzymes.

Conclusion

9. Claims 1, 3-8, 10, 17 and 18 are rejected.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Shibuya, whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. J. Douglas Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Art Unit 1639